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Randomised adjuvant trial comparing two dose intensities of epirubicin and cyclophosphamide (EC) in high-risk breast cancer

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Due to bad prognosis therapy of breast cancer patients at high risk of recurrence and death remains challenging. Dose-intensification and dose-density are promising concepts to improve survival of these women.

Purpose: Our trial served the purpose, to define the role of a dose-intense and dose-dense regimen in adjuvant breast cancer treatment.

Methods: Between 3/1993 and 8/1997 we randomised 182 patients with high-risk breast cancer defined by >9 positive axillary lymphnodes or extracapsular involvement to either 4 cycles EC 120/600 mg/m" q2w with G-CSF-support (HDI-EC) or 4 cycles EC 90/600 mg/m" q3w followed by three cycles CMF (EC/CMF).

Results: At present 174 patients are evaluable. During a median follow-up of 24 months (range 3 to 54 months) 38 recurrences and 18 deaths were observed. Multivariate analysis revealed progesteron receptor and nodal status (1–9 vs. 10+) as significant prognostic factors. Intention to treat evaluation, performed by Kaplan-Meier estimates, showed a mean DFS of 44 months for patients receiving HDI-EC versus 37 months for patients receiving EC/CMF (p = 0.03), OAS was 49 versus 44 months (p > 0.05). Benefit was seen in patients with 1 to 9 positive lymphnodes as well as patients with 10 or more positive lymphnodes. Hematologic toxicity in the HDI-EC arm was present as leucopenia WHO grade III in 13%, grade IV in 8.3% and thrombopenia WHO grade III/IV in 1.2% of all cycles. Anemia was found in 2.8% of all patients receiving HDI-EC. Non hematologic toxicity mainly consisted of nausea (53%), vomitus (34%) and alopecia (100%). One treatment related death was due to acute dilatative cardiomyopathia at a cumulative Epirubicin dose of 480 mg/m".

Conclusions: Regarding the short follow-up we conclude, that HDI-EC is feasible regimen with considerable shorter time of treatment. DFS is significantly superior at present, longer follow-up will reveal, whether this favourable trend will persist.

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Comparison of 3 versus 6 cycles CMF in node positive breast cancer patients based on 10 years follow-up

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Purpose: In 1984 the GBSG started a multicenter randomized trial to compare in 2 × 2 study the effectiveness of three versus six cycles CMF and the additional effect of tamoxifen.

Materials and Methods: During 5 years, 41 institutions randomized 473 patients. In the first analysis, based on follow-up until March 1992, no significant difference in recurrence free survival (RFS) was observed for duration of chemotherapy (Schumacher et al. 1994; JCO, 12: 2086–2093). Based on follow-up until December 1997 an updated analysis for RFS and overall survival (OS) will be presented.

Results: Based on 271 events for RFS and 226 deaths, the estimate of the relative risk for the effect of 3 versus 6 cycles CMF is 0.96 (95% confidence interval 0.76–1.22) for RFS and 0.94 (0.72–1.22) for OS. Adjustment for prognostic factors has hardly any influence on these estimates..

Conclusion: The results of this study support a reduction of duration of CMF to cycles only.

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Doxorubicin (A) followed by docetaxel (T) versus doxorubicin + docetaxel (AT) in the adjuvant treatment of breast cancer (BC)

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We evaluated the two following regimens: 1) A 75 mg/m^2 q 3 wks × 3 → T 100 mg/m^2 q 3 wks × 3 → CMF i.v. days 1 + 8 q 4 wks × 3; 2) AT (50/75 mg/m^2) q 3 wks × 4 → CMF (as for 1) × 4. A factor to note is that, cumulative doses of A and T in the two arms were nearly identical. Pts with N-positive BC aged ≤ 70 y.o. were eligible.

Data regarding A → T and AT are compared below. Data related to CMF are not reported.

	A → T	AT
N° treated pts/.N° cycles	20/118	29/95
% of pts withdrawn	5	7
% cycles with RDI < 75%	1	1
% pts reporting:		
– vomiting/stomatitis (%G3)	60 (5)/65 (20)	31 (3)/52 (3)
– skin/neuro-toxicity (%G3)	35 (5)/55 (–)	17 (–)/17 (–)
– neutropenic fever	30	48

These data suggest that when A and T are given sequentially rather than in combination, there is a higher incidence of single drug-related side effects and a lower incidence of neutropenic fever. Both strategies are feasible in the adjuvant treatment of BC. A comparison in terms of activity is ongoing in a phase III trial.

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Doxorubicin vs CMF in the adjuvant tratment of high risk breast cancer

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This trial was activated to compare the efficacy of Doxorubicin vs CMF in adjuvant treatment locally-advanced breast cancer T1-2N2M0, T3N0-2M0. From 1985 to 1990, 349 pts aged 27–57 years, who had undergone preoperative radiation therapy (60 Gy to the breast and 40 Gy to the axillary lnd) followed by modified radical mastectomy, were randomized to receive either Doxorubicin 50 mg/m^2, iv, on day 1 and 8, every 4 weeks, to total dose 500 mg/m^2 (165 pts), or classical CMF regimen up to 6 cycles (184 pts). Mean duration of follow-up was 68.8 months. The overall (OS) 5-years survival rate was 73% in the Doxorubicin group and 62% in CMF group (P = 0.12). The disease free (DFS) survival was 62.8% in the Doxorubicin group and 55% in the CMF group (P = 0.06).

Only in subgroup of pts with tumor pN2 was estimated significant improvement DFS in Doxorubicin group (86.3%) vs CMF (58%), P < 0.01. But this phenomena requires further study with more number of events.

In spite of appreciable absolute difference in rates of OS (11%) between treatment groups, it has statistically doubtful.

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A randomized phase III trial of adjuvant endocrine therapy with tamoxifen for one year (TAM1) vs tamoxifen for two years (TAM2) in postmenopausal high risk patients with estrogen receptor positive or estrogen receptor unknown breast cancer. A DBCG study

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Purpose: To evaluate whether adjuvant TAM2 is superior to TAM1 using disease free (DFS) and overall survival (OS) as end points in postmenopausal high risk patients with operable breast cancer.

Methods: The study was conducted in the years 1990 to 1996. Following surgery and adjuvant radiotherapy postmenopausal high risk patients with estrogen receptor positive or estrogen receptor unknown breast cancer

were randomized to receive adjuvant endocrine treatment. Patients were offered tamoxifen 30 mg od for one year vs tamoxifen 30 mg od for two years vs tamoxifen 30 mg od for six months followed by megestrol acetate 160 mg od for six months. The third arm was closed early due to side effects leaving 900 patients randomized to TAM1 and 879 patients randomized to TAM2.

Results: The study was well balanced with regard to type of surgery and prognostic factors: age, tumor size, number of positive nodes, tumor type, and degree of anaplasia. Analysis of DFS in February 1998 revealed 263 events in TAM1 and 255 events in TAM2 with corresponding five year DFS of 59.6% and 59.0% (ns). Analysis of OS showed 171 failures in TAM1 and 162 failures in TAM2 with corresponding five year OS of 71.4% and 73.1% (ns). Data on secondary cancers in the two treatment arms will be presented.

Conclusions: This study in operable postmenopausal high risk breast cancer patients did not find adjuvant tamoxifen for two years superior to tamoxifen for one year.

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Adjuvant Goserelin depot in premenopausal women with early breast cancer: Ovarian function, bone mineral density and survival. Preliminary data

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Ovary suppression with Goserelin depot is alternative to ovarian ablation: in metastatic breast cancer Goserelin depot yelded objective response in 36% of patients. Ovarian ablation in women aged under 50 was associated with 6% fewer recurrences or deaths after 15 years. Studies are ongoing in order to evaluate the effectiveness of Goserelin depot as adjuvant treatment in the prevention of relapse and reduction in mortality.

We report our experience about 75 premenopausal patients with early breast cancer treated after surgery with Goserelin depot 3.6 mg subcutaneously every 28 days for two years. Median age was 43 years (range 31–50), all patients had regular menses, 36 patients were N+ and 39 were N−. ER status was positive in all patients but one in which was unknown.

One patient had bilateral breast cancer.

Owing to administration of Goserelin depot amenorrhea occurred after the first depot in 11 patients and after the 2nd depot in 64 women.

Spotting was observed in 8 patients and stopped after 10 depots.

At the end of 26 depots regualr menses resumed in most patients (73%), on average after 5.3 months.

Weight gain was observed in 61% of patients, in 28.1% of patients weight was unchanged, weight loss occurred in the remaining women. All patients complained of hot flushes, sweating and impairment of libido. Metrorrhagia occurred in 3 patients at the end of therapy: 2 patients underwent hysterectomy. A decline in Bone Mineral Density was observed in patients studied with Dual Energy X-ray Absorptiometry (DEXA). A second primary tumor occurred in four patients: myeloid chronic leukemia, kidney cancer, oat cell carcinoma, second primary breast cancer. At a median follow-up of 51 months overall survival was 88% and disease free survival 77%.

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Ovarian toxicity of breast cancer chemotherapy

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The aim of this study was to provide individual information, to a patient (pt) who is going to receive adjuvant or neoadjuvant chemotherapy for operable breast cancer, about the probability she may experience amenorrhea. From November 1988 to August 1997, 249 premenopausal patients underwent chemotherapy for breast cancer in neoadjuvant or ajuvant settings. Chemotherapy regimens combined Fluoro-uracil 500 mg/m^2, Epirubicin 50 to 100 mg/m^2 and Cyclophosphamide (CPM) 500 mg/m^2 (FEC) delivered every 3 weeks in 6 cycles.

Premenopausal status was defined as regular menses with last menses occurring less than 60 days. Amenorrhea was defined as discontinuation of menses for more than 60 days. Age of premenopausal patients ranges from 23 yrs to 55 yrs (median 43 yrs). One hundred seventy one out of 249 patients (70%) experienced amenorrhea while on chemotherapy delivering a CPM mean cumulative dose of 2.9 g/m^2. No amenorrhea was observed in 12 patients aged of less than 32 yrs. In the age group 32–37 yrs (45 pts) 15% experienced amenorrhea (always reversible), 38–39 yrs (18 pts) 55% amenorrhea (87% reversible), 40–41 yrs (24 pts) 79% (94% reversible), 42–47 yrs (109 pts) 88% (42% reversible) and from 48 yrs (41 pts) 95% presented amenorrhea (92% permanent). CPM mean dose to onset of amenorrhea and time to amenorrhea correlate conversely with age: from 2 g/m^2 (in 87 days) in age group 32–37 yrs to 0.8 g/m^2 (33 days) from 48 yrs. Permanent amenorrhea depends on CPM dose received after the onset of amenorrhea, when the ratio: dose at amenorrhea/cumulative dose is superior to 0.5 the probability of resuming menses is very high ($p = 0.01$) for patients aged 40 and over. In conclusion, our results allow us to inform a patient what is the risk for her to experience amenorrhea and the probability to resume or not menses, according to her age and to the CPM dose to be administered.

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Early treatment of metastatic breast cancer patients after increase of CEA and CA15-3 serum levels

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Purpose: After an increase of CEA and/or CA15-3 serumlevels during follow-up in breast cancer patients, more than 80% will develop metastases within one year.

Methods: CEA and CA15-3 were measured in monthly intervals after primary surgery because of breast cancer. In a prospective randomized trial we evaluated if an early hormonal treatment with high-dose gestagens, starting at first tumormarker increase when metastases were clinically not detectable, improves the relapse-free survival. The analysis of survival times was performed accordcing to the Kaplan-Meier method.

Results: There was a significant difference in relapse-free survival between the treatment group [0.71; 0.53–0.89] and the untreated control group [0.25; 0.09–0.41] ($p < 0.01$).

Conclusion: Therefore the early beginning of systemic therapy will be a strategy for the prolongation of survival in breast cancer patients. Serial measurements of CEA and CA15-3 should be an integral part of routine follow-up examinations in high-risk breast cancer patients for the early detection of progressing metastatic disease.

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Docetaxel toxicity and activity in anthracycline-pretreated metastatic breast cancer (MBC)

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From July 1995 to date 55 patients (pts) with MBC were treated with docetaxel. Patient data: median age: 51 yrs (range: 28–68); median PS: 0 (range: 0–3); n. of metastatic sites: 1–2: 39 pts; ≥3: 16 pts; dominant visceral site of disease: 62% of pts. Previous treatments: adjuvant chemotherapy only: 11; chemotherapy for advanced disease only: 21; both 23 pts. All pts were pretreated with anthracyclines (A) and 10 were also pretreated with paclitaxel (PT). Four out of 55 pts had progressed while on A (refractory), 18 had progressed within 6 months from the completion of an adjuvant A or had SD as best response to A for metastatic disease (resistant). The remaining 33 pts were considered sensitive to A. Docetaxel was administered at the dose of 100 mg/m^2 q 3 weeks as a 1 h i.v. infusion. Two different pre- and post-medication schedules were used: oral prednisone 50 mg hours −13, −7, −1, +1, +12 and then bid in the following three days (29 pts), or i.m. dexamethasone 8 mg/d days −1, 0, 1 and 2 along with ondansetron 8 mg i.v. on day 0 (26 pts). The latter cohort of pts also received prophylactic lenograstim 150 μg/m^2 every other day for 4 doses starting on day 4. Fifty-three pts were evaluable for response, and 55 for toxicity. Overall response rate: 53% (24 PRs, 4 CRs); SD: 32%; PD: 15%. As for A status, an objective response (OR) was observed in 2/4, 8/17 and 18/32 refractory, resistant and sensitive evaluable pts, respectively. In the 10 pts pretreated with PT 5 ORs (50%) were observed. Liver disease responded in 16/25 pts (5 CRs, 11 PRs; 64%). G 3–4 neutropenia and neutropenic fever were significantly higher in pts who did not receive prophylactic G-CSF (52% and 9% of 137 evaluable cycles vs 3.5% and 0% of 114 evaluable cycles, $p = .0001$ and $p = .01$, respectively). No significant differences were observed in non hematological toxicity, except for the incidence of moderate to severe fluid retention syndrome, which was higher in the group that received oral corticosteroids (24% vs. 4%, $p = .08$, respectively). Our experience confirms the high activity and manageable toxicity of docetaxel for the treament of MBC even in A, as well as in PT-pretreated pts.